Dynamic contrast-enhanced magnetic resonance imaging perfusion characteristics in meningiomas treated with resection and adjuvant radiosurgery

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OBJECTIVE There is a need for advanced imaging biomarkers to improve radiation treatment planning and response assessment. T1-weighted dynamic contrast-enhanced perfusion MRI (DCE MRI) allows quantitative assessment of tissue perfusion and blood-brain barrier dysfunction and has entered clinical practice in the management of primary and secondary brain neoplasms. The authors sought to retrospectively investigate DCE MRI parameters in meningiomas treated with resection and adjuvant radiation therapy using volumetric segmentation.

METHODS A retrospective review of more than 300 patients with meningiomas resected between January 2015 and December 2018 identified 14 eligible patients with 18 meningiomas who underwent resection and adjuvant radiotherapy. Patients were excluded if they did not undergo adjuvant radiation therapy or DCE MRI. Demographic and clinical characteristics were obtained and compared to DCE perfusion metrics, including mean plasma volume (v_p), extracellular volume (v_e), volume transfer constant (K^{trans}), rate constant (k_{ep}), and wash-in rate of contrast into the tissue, which were derived from volumetric analysis of the enhancing volumes of interest.

RESULTS The mean patient age was 64 years (range 49–86 years), and 50% of patients (7/14) were female. The average tumor volume was 8.07 cm³ (range 0.21–27.89 cm³). The median Ki-67 in the cohort was 15%. When stratified by median Ki-67, patients with Ki-67 greater than 15% had lower median v_p (0.02 vs 0.10, $p = 0.002$), and lower median wash-in rate (1.27 vs 4.08 sec⁻¹, $p = 0.04$) than patients with Ki-67 of 15% or below. Logistic regression analysis demonstrated a statistically significant, moderate positive correlation between v_e and time to progression ($r = 0.49$, $p < 0.05$). Furthermore, there was a moderate positive correlation between K^{trans} and time to progression, which approached, but did not reach, statistical significance ($r = 0.48$, $p = 0.05$).

CONCLUSIONS This study demonstrates a potential role for DCE MRI in the preoperative characterization and stratification of meningiomas, laying the foundation for future prospective studies incorporating DCE as a biomarker in meningioma diagnosis and treatment planning.

<https://thejns.org/doi/abs/10.3171/2019.3.FOCUS1954>

KEYWORDS DCE MRI; meningioma; radiosurgery; perfusion

MENINGIOMAS are the most common primary intracranial tumors. Meningiomas are typically treated with surgery and adjuvant radiation in cases of subtotal resection and/or higher histopathological grade.^{14,16} Postoperative MRI appearance is the gold standard for adjuvant treatment planning, specifically stereotactic radiosurgery (SRS). However, MRI can have limited sensitivity and specificity in cases demonstrating an infil-

trative pattern of growth, osseous or parenchymal invasion, and/or postsurgical or postradiation change. Furthermore, a wide variety of intracranial lesions, both benign and malignant, have an MRI appearance that can closely mimic meningioma.¹⁷ Moreover, conventional MRI does not reliably differentiate between subtypes of meningioma. Thus, there is a need for advanced imaging biomarkers to improve radiation treatment planning and response assess-

ABBREVIATIONS BED = biologically effective dose; DCE = dynamic contrast-enhanced; k_{ep} = rate constant; K^{trans} = volume transfer constant; rCBV = relative cerebral blood volume; SRS = stereotactic radiosurgery; TTP = time to progression; v_e = extracellular volume; v_p = mean plasma volume.

SUBMITTED January 31, 2019. **ACCEPTED** March 25, 2019.

INCLUDE WHEN CITING DOI: 10.3171/2019.3.FOCUS1954.

ment. T1-weighted dynamic contrast-enhanced (DCE) perfusion MRI (DCE MRI) allows quantitative assessment of tissue perfusion and blood-brain barrier dysfunction, and has entered clinical practice in primary and secondary brain neoplasms.⁷ In meningioma, DCE MRI has been proposed as a tool to distinguish between lower- and higher-grade tumors and has also been utilized to differentiate meningiomas from dural-based metastases.^{12,19,20} Moreover, peritumoral edema surrounding atypical meningiomas has been shown to have distinct perfusion characteristics compared with benign meningiomas.²⁰ Based on this prior work, we sought to retrospectively investigate DCE MRI parameters in meningiomas treated with resection and adjuvant radiation therapy and hypothesized that DCE perfusion MRI may be an informative biomarker in radiation therapy response assessment.

Methods

Patients

In this institutional review board approved—, Health Insurance Portability and Accountability Act compliant—retrospective study, patients eligible for analysis were selected using retrospective chart review applying the following selection criteria. Based on a database of pathology-proven resected meningiomas, more than 300 patients who underwent resection between January 2015 and December 2018 were screened for eligibility. Patients were excluded if they did not undergo adjuvant radiation therapy and did not undergo DCE MRI, resulting in 14 eligible patients with 18 meningiomas. In all patients, a histopathological and molecular diagnosis was confirmed by experienced, board-certified neuropathologists.

Demographic and clinical characteristics were obtained from clinical chart review, including tumor location (skull base vs other location), Simpson grade, WHO grade, Ki-67 labeling index, radiation therapy type and dose, and time to progression (TTP). The biologically effective dose (BED) of radiation was calculated using an online calculator (<https://www.mdcalc.com/radiation-biologically-effective-dose-bed-calculator>) (Table 1).¹⁸

Imaging

All patients underwent MRI of the brain on 1.5- or 3-Tesla clinical scanners (Skyra, Aera, Biograph mMR, Siemens Healthcare; Discovery 750w, Signa HDxt, GE Healthcare), which included axial T1-weighted (TR/TE 550–700 μ sec/7–10 μ sec, slice thickness 3–5 mm) or 3D T1-weighted SPACE (TR/TE 600–700 μ sec/11–19 μ sec, 120° flip, slice thickness 1 mm), axial T2-weighted (TR/TE 3200–4000 μ sec/93–98 μ sec, slice thickness 5 mm), and axial T2-weighted FLAIR or 3D T2-weighted FLAIR (TR/TE 6300–8500 μ sec/394–446 μ sec, 120° flip angle, slice thickness 1 mm). T1-weighted DCE MRI was performed and available for analysis in all of the cases (TR 4 μ sec, TE 1–2 μ sec, flip angle 13°, slice thickness 3 mm, 44 slices to cover the entire lesion volume, 24 phases with 4 phases before and 20 phases after intravenous bolus administration of 0.1 mL/kg gadopentetate).

DCE Perfusion Analysis

Olea Medical 3.0 software was utilized for DCE MRI

processing and analysis (Figs. 1 and 2). Analysis was performed on volumes of interest that included the entire enhancing tumor volume, inclusive of all slices (Fig. 1). DCE perfusion metrics, including mean plasma volume (v_p), extracellular volume (v_e), volume transfer constant (K^{trans}), rate constant (k_{ep}), and wash-in rate of contrast into the tissue were derived from volumetric analysis of the enhancing volumes of interest.³

Statistical Analysis

Statistical analysis was performed utilizing Graph-Pad Prism version 7. Patients were stratified by Simpson grade, pathological WHO grade, Ki-67, tumor location, and SRS dosing strategy, and the Mann-Whitney U-test was performed to identify statistically significant differences between DCE parameters. ANOVA was performed to determine statistical differences when stratification into 3 subgroups was needed (WHO grade, SRS dosing strategy). Linear regression and Spearman correlation were also used to investigate the differences in permeability parameters when compared with TTP. The plots were made using ggplot2 in RStudio version 1.1.463 with R version 3.5.2 (r-project.org; Fig. 3).

Results

Clinical and demographic characteristics of the study population and DCE parameters are outlined in Table 1. A total of 18 tumors in 14 patients were evaluated. Mean patient age was 64 years (range 49–86 years), and 50% of patients (7/14) were female. The average tumor volume was 8.07 cm³ (range 0.21–27.89 cm³).

When stratifying by Simpson grade (I, II, and III vs IV and V), there was a trend toward higher median k_{ep} , v_p , and K^{trans} in the higher Simpson grade group; however, this did not reach statistical significance (Table 2). When stratifying by location, there was a trend toward higher median wash-in rate in skull base tumors. When stratifying by SRS dosing into fractionated versus hypofractionated tumors (with the latter group including tumors treated with other types of radiation therapy), differences in median k_{ep} , K^{trans} , v_e , v_p , and wash-in rate values did not reach statistical significance, although there was a trend for higher v_p in the hypofractionated group compared with the fractionated group (0.03 vs 0.09, $p = 0.35$; Table 2). When stratifying into 3 subgroups, with non-SRS radiotherapy (such as brachytherapy and proton-beam radiation therapy), the p value for v_p decreased; however, it did not reach statistical significance ($p = 0.06$) (Table 3).

The median Ki-67 in the cohort was 15%. When stratifying by median Ki-67, patients with Ki-67 greater than 15% had lower median v_p (0.02 vs 0.10, $p = 0.002$), and a lower median wash-in rate (1.27 vs 4.08 sec⁻¹, $p = 0.04$) than patients with Ki-67 of 15% or below. The median Ki-67 was 15% for this cohort. Logistic regression analysis demonstrated a statistically significant, moderate positive correlation between v_e and TTP ($r = 0.49$, $p < 0.05$). There was a moderate positive correlation between K^{trans} and TTP, which approached, but did not reach, statistical significance ($r = 0.48$, $p = 0.05$; Fig. 3). Furthermore, the regression analysis demonstrated significant correlation

TABLE 1. Patient demographics, clinical characteristics, and DCE perfusion metrics

Age (yrs), Sex	Location	Simpson Grade	Radiation Dose or Type (BED)*	Ki-67 (MIB-1) Labeling Index	WHO Grade	Time to Recurrence (mos)	k_{ep}	K^{trans}	V_e	V_p	Wash-In Rate (sec ⁻¹)	Tumor Vol (cm ³)
52, F	Rt lateral sphenoid wing	III	24 Gy, 3 fx (75)	10–20%	III	15	0.38	0.24	0.64	0.09	13.74	0.63
77, F	Rt parietal	IV	60 Gy, 30 fx (92)	20%	III	16	0.96	0.33	0.34	0.02	1.65	0.41
49, M	Lt nasal cavity	III	PBRT	>30%	III	16	0.95	0.29	0.33	0.10	4.78	7.26
49, M	Lt ASB/max sinus	III	PBRT	>30%	III	9	1.09	0.21	0.23	0	20.07	27.89
63, M	ASB	V	52.2 Gy, 29 fx (80)	8.52%	I	9	0.5	0.26	0	0.23	2.71	9.84
57, M	Rt frontal	I	Brachytherapy	30–40%	III	11	0.25	0.04	0.15	0.03	0.83	3.08
57, M	Rt temporal	I	Brachytherapy	30–40%	III	11	0.26	0.06	0.22	0.05	0	15.78
62, F	Rt frontal	I	54 Gy, 30 fx (83)	10%	II	20	0.7	0.23	0.30	0.10	5.27	0.21
74, M	ASB	IV	60 Gy, 30 fx (92)	>50%	III	11	0.55	0.07	0.10	0.01	0.28	2.11
60, M	Lt frontal	I	54 Gy, 30 fx (90)	8–10%	II	1	0.30	0.10	0.29	0.03	1.63	0.64
54, F	Rt FM	V	25 Gy, 5 fx (58)	3%	I	27	0.84	0.29	0.25	0.07	2.16	0.77
54, F	Rt CPA	V	25 Gy, 5 fx (58)	2–3%	I	27	1.23	0.49	0.37	0.23	6.63	2.00
86, M	ASB	III	60 Gy, 30 fx (92)	20%	II	12	1.32	1.14	0.68	0.02	2.12	19.64
79, F	Lt frontal	I	54 Gy, 30 fx (83)	17%	II	None	0.24	0.02	0.11	0.02	0.89	5.03
86, M	ASB	IV	27 Gy, 3 fx (92)	<5%	II	12	1.13	0.16	0.07	0.46	28.52	5.25
70, F	Lt frontal	IV	PBRT	12%	II	59	0.84	0.37	0.43	0.11	2.45	10.17
62, F	Rt frontal convexity	IV	45 Gy, 15 fx (81)	15%	II	9	1.25	0.42	0.33	0.10	2.88	8.44
62, F	Rt sphenoid wing	IV	54 Gy, 30 fx (83)	15%	II	27	0.96	0.29	0.31	0.10	5.93	18.39
Mean							0.76	0.28	0.29	0.10	5.70	8.07
Median							0.84	0.25	0.295	0.08	2.58	5.25
SD							0.38	0.25	0.18	0.11	7.62	8.07

ASB = anterior skull base; CPA = cerebellopontine angle; FM = frontal meningioma; fx = fractions; max = maxillary; PBRT = proton-beam radiation therapy.

*Biologically effective dose (BED) calculated using <https://www.mdcalc.com/radiation-biologically-effective-dose-bed-calculator>.

FIG. 1. Representative posttreatment DCE MR images in a 62-year-old woman with recurrent WHO grade II meningioma of the right sphenoid wing with prior craniotomy and fractionated radiation therapy. Axial T1-weighted postcontrast image (A) and overlaid semiautomatic volume of interest (B), K^{trans} map (C), and v_p map (D).

irrespective of WHO grade (Fig. 3). The remaining DCE parameters did not demonstrate statistically significant correlation with TTP.

Discussion

In this study, we sought to characterize DCE MRI parameters in meningiomas treated with resection and adjuvant radiation therapy. We analyzed clinical and treatment-related information including Simpson grade, tumor location, pathological findings, including Ki-67 index, radiotherapy dosing data, and time to progression of disease. Our findings highlight a potential role for DCE MRI in the preoperative characterization and stratification of meningiomas and lay the foundation for a prospective study incorporating DCE as a biomarker in meningioma diagnosis and treatment planning. Importantly, time to progression after radiation therapy demonstrated a moderate positive correlation, which was statistically significant in the case of v_e and approached statistical significance in the case of K^{trans} , indicating that these parameters may be helpful in predicting progression in meningiomas on posttreatment surveillance imaging.

Previous work suggested that DCE MRI may facilitate noninvasive preoperative predictions of intracranial tumor characteristics and may have a potential to allow prognostic decisions and to guide therapies.^{1,8} DCE MRI has also been studied for its potential utility in differentiating tumors by type and grade, as the spatial properties and

FIG. 2. Representative posttreatment DCE MR images in a 49-year-old man with multiply recurrent WHO grade III meningioma centered in the left maxillary sinus with multiple prior resections and multiple courses of radiation therapy. Axial T1-weighted postcontrast image (A) and overlaid semiautomatic volume of interest (B), K^{trans} map (C), and v_p map (D).

function of the tumor vasculature differ in these circumstances.^{4,11,13,15} In mixed cohorts of intracranial tumors that include meningiomas, gliomas, and metastases, it has been shown that differences in vessel permeability, as captured by perfusion MRI, can help differentiate between meningiomas and intraaxial tumors.^{2,10,11,13}

Several studies have previously investigated the potential role of DCE MRI in the characterization of meningiomas. Thus, K^{trans} was found to have utility in distinguishing atypical meningiomas from typical meningiomas on preoperative DCE MRI.¹⁹ DCE MRI was also proposed as a biomarker in the diagnosis of rare meningioma variants such as lipomatous variant of metaplastic meningioma and a microcystic meningioma.⁶ Dynamic susceptibility contrast MRI-derived relative cerebral blood volume (rCBV) has been proposed as a biomarker for meningiomas, given data suggesting that rCBV correlated with vascular endothelial growth factor (VEGF) expression and tumor grade.⁵ A recent study suggested that an enhancing cystic lesion with a normalized rCBV greater than 10.3 cm³ or a K^{trans} greater than 0.88 min⁻¹ should prompt radiologists and surgeons to consider the diagnosis of the rare microcystic meningioma rather than traditional WHO grade I meningioma or high-grade glioma in surgical treatment planning. However, not all data confirm the predictive utility of DCE MRI, which remains an area of active research.⁹

We present here the results from a unique cohort of patients with meningiomas who underwent resection, adjuvant radiotherapy, and DCE MRI and validate the potential utility of DCE MRI in this clinical context. Limitations of

FIG. 3. DCE parameters in meningiomas treated with resection and adjuvant radiosurgery: correlation with TTP. **Left:** Logistic regression analysis of K^{trans} and TTP. **Right:** Logistic regression of v_e and TTP. Each data point represents a tumor; color indicates WHO grade.

this study include the small sample size and retrospective methodology. Furthermore, the median Ki-67 of this cohort was 15%, indicating an inherent bias toward more aggressive meningiomas. This also implies that DCE MRI was done on more aggressive tumors, likely as a problem-solving tool in treatment planning. Future directions include validating our findings in a prospective cohort including pre- and posttreatment surveillance DCE MRI, allowing for the continued development of DCE MRI as a biomarker of diagnosis and treatment response assessment of meningioma, thereby improving patient outcomes.

Conclusions

In this study, we aimed to characterize DCE MRI pa-

rameters in meningiomas treated with resection and adjuvant radiation therapy. This is the first study of a cohort of patients with meningiomas who have undergone resection and adjuvant radiotherapy that aims to validate the potential usefulness of DCE MRI in this clinical context. Importantly, despite the small sample size, time to progression after radiation therapy demonstrated a moderate positive, statistically significant correlation with v_e and a moderate positive correlation with K^{trans} that approached statistical significance, indicating that these parameters may be helpful in predicting progression in meningiomas on posttreatment surveillance imaging. Furthermore, when stratified by Ki-67, tumors demonstrated statistically significant differences in v_p and wash-in rate, which prompts the potential utility of v_p and wash-in rate as diagnostic markers

TABLE 2. DCE MRI parameters stratified by Simpson grade, tumor location, Ki-67, and radiotherapy dosing strategy

	No. of Meningiomas	DCE MRI Parameter*				
		k_{ep}	K^{trans}	v_e	v_p	Wash-In Rate (sec ⁻¹)
Simpson grade						
I, II, or III	9	0.38	0.21	0.29	0.03	2.12
IV or V	9	0.96	0.29	0.31	0.1	2.71
p value		0.09	0.08	0.81	0.07	0.55
Tumor location						
Skull base	9	0.96	0.26	0.25	0.09	5.93
Not skull base	9	0.7	0.23	0.3	0.05	1.65
p value		0.13	0.44	0.78	0.75	0.06
Ki-67						
≤15%	10	0.84	0.28	0.31	0.1	4.08
>15%	8	0.75	0.14	0.23	0.02	1.27
p value		0.54	0.2	0.6	0.002	0.04
SRS fractionation						
Fractionated	9	0.7	0.26	0.3	0.03	2.12
Hypofractionated/other	9	0.84	0.24	0.25	0.09	4.78
p value		0.98	0.86	0.81	0.35	0.26

The Mann-Whitney U-test was performed to determine statistical significance.

* Parameter values are medians.

TABLE 3. DCE parameters stratified by radiotherapy dosing strategy

DCE MRI Parameter	Dosing Strategy			p Value
	Fractionated (n = 9)	Hypofractionated (n = 4)	Other (n = 5)	
k_{ep}	0.70	0.84	0.99	0.71
K^{trans}	0.26	0.21	0.31	0.70
V_p	0.03	0.05	0.17	0.06
V_e	0.30	0.23	0.40	0.86
Wash-in rate (sec ⁻¹)	2.12	2.45	10.19	0.08

ANOVA was performed to determine statistical significance.

in preoperative treatment planning. Our findings indicate a potential role for DCE MRI in the preoperative characterization and stratification of meningiomas and lay the foundation for a prospective study incorporating DCE as a biomarker in meningioma diagnosis and treatment planning.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ivanidze, Chidambaram, Roytman. Acquisition of data: Ivanidze, Chidambaram, Pannullo, Pisapia, Liechty, Magge, Ramakrishna, Stieg, Schwartz. Analysis and interpretation of data: Ivanidze, Chidambaram, Pisapia, Liechty. Drafting the article: Ivanidze, Chidambaram, Pannullo, Pisapia, Liechty, Magge, Ramakrishna. Critically revising the article: Ivanidze, Chidambaram, Pannullo, Roytman, Pisapia, Liechty, Magge, Ramakrishna. Reviewed submitted version of manuscript: all authors. Statistical analysis: Ivanidze, Chidambaram, Liechty. Administrative/technical/material support: Pisapia, Liechty. Study supervision: Ivanidze, Chidambaram, Pannullo.

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